THE COMING REVOLUTION FOR COATINGS SCIENCE: HIGH THROUGHPUT SCREENING FOR FORMULATIONS

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ABSTRACT

A revolution is needed in coatings science to respond to a tidal wave of requirements being put onto the development chemists. Development groups see the impact in increasing number of available raw materials, increasing complexity of formulations, intolerance of raw material variability, complexity of end use specifications and of course in performance expectations. Concurrently these same groups are being pressured to reduce costs, reduce personnel and most of all reduce development time. There is no time available to do all of the required testing. The industry needs to radically alter its approach to product development. A glimpse of the future possibilities can be seen in the pharmaceutical industry, they have already gone through a revolution in the way they do development. There the use of high throughput and combinatorial chemistry techniques is widespread yielding orders of magnitude increases in productivity for the screening of potential drug candidates. Adoption and adaptation of these techniques to coatings science will allow our industry to respond to the need to evaluate a large parameter space in the minimum amount of time.

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Introduction

There is a revolution sweeping through the pharmaceutical and chemical industries – the banners of this revolution claim total change for those who embrace it, unimaginable increases in productivity, shortening of development times and breakthroughs from every experiment. The signs are all around us, the articles, the symposia, the advertisements that promise the world. There is a real concern that companies and even a country's industries that do not adapt to it will no longer flourish or may not even survive. The revolution has multiple names:

- Combinatorial Chemistry
- Combinatorial Methodology
- High Throughput Screening
- High Throughput Experimentation
- Parallel Synthesis

It is a confusing revolution. There are a plethora of methods that can be applied. Nomenclature in this field is very complex, many names are used interchangeably. The basic concepts are fairly straightforward but of course the devil is in the details. Many academics and senior scientists rail against its use, saying it effectively reduces science to the work of machines – casting this technology as the moral equivalent of a room full of monkeys with typewriters cranking out novels.

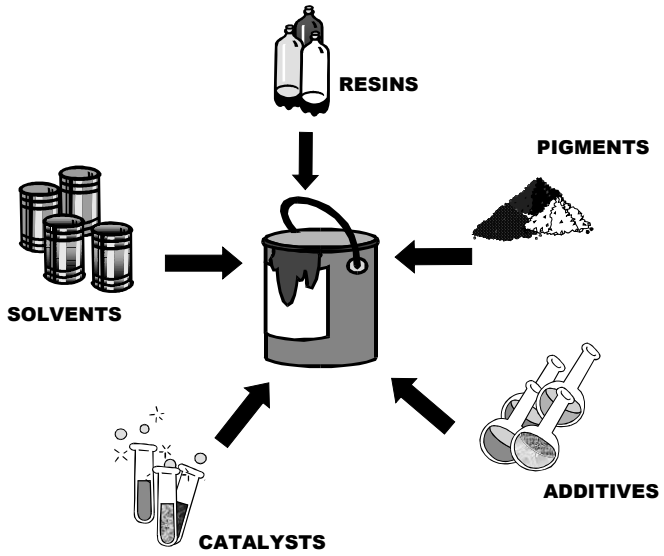
Even with the hype and dissention, it is a process of change that is worth paying attention to. Development leaders and business executives should be concerned that their competition will use these methods to develop products that make greater use of inexpensive raw materials, are more highly optimized and are developed in less time.

To understand and appreciate the possibilities of high throughput technologies for the Coatings Industry, we will venture to comment on:

- The current situation and practices in coatings laboratories.
- The lessons from drug discovery's successes and methods.
- The situation in materials science.
- The application of these techniques to coatings science.
- The limitations and applicability of the technology.

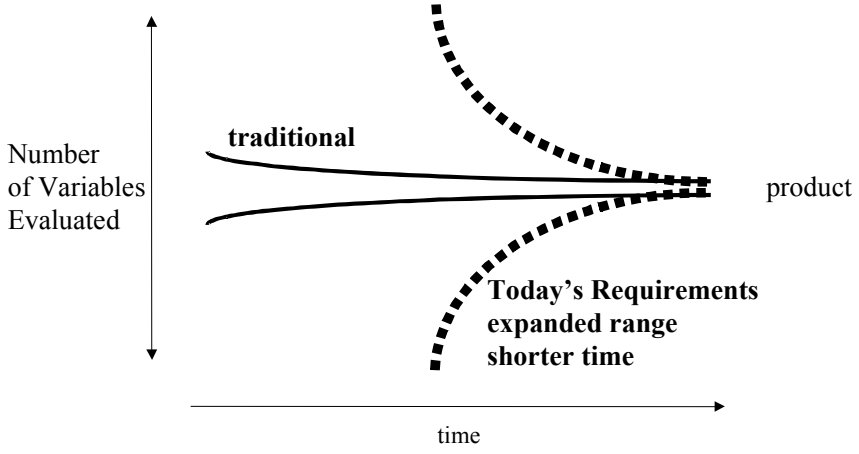
The Current Situation in Coatings Laboratories

Over the last 50 years there has been little change to the core methodology of how we look at new chemistries and compounds. For the most part paint is made through Edisonian trial and error: Make a paint; throw it against the wall; and see if it sticks, make some change and throw it again. Yes, there have been great advances in analytical methods, and yes some practitioners have adopted the use of Design of Experiments and statistical analysis. But for the most part we still do each step by hand, working on individual samples, or maybe up to a dozen formulations at the same time if the bench person is very good.



Formulating coatings is often viewed as an art with a little science thrown in. Coatings are made from combining a number of components in the right ratios in a reproducible way. For each of the components there are a large number of choices in chemistry, suppliers and grades – the choices made of product type and grade can have profound impact on the final properties of the coating. These choices are compounded by having to consider variations within each of the products – each has a certain specification range and the performance of the end product may be greatly affected by variations within that range.

Development groups across the industry are also seeing a rising complexity in the testing and evaluation of coating performance. This results from the increasing number and complexity of end use specifications, to include a large number of customer specific ones. This also arises from ever-increasing performance expectations and the cost of not meeting those. At the same time there is pressure to reduce costs, personnel and most all development time. As result there is not the time or personnel available to spend on thoroughly understanding new products using existing techniques. As a consequence, if a new product or ingredient does not show an immediate benefit it will not be fully evaluated.



One can imagine that the following sequence could take place within any number of large coatings related corporations:

1. A synthetic chemist develops a radically new coreactant for a melamine crosslinked system. At first glance, the new product appears to bring a performance or cost advantage to the company. It is provided to a formulator.
2. The formulator finds an existing formulation containing between 8-12 discrete ingredients that is in need of improvement. Or maybe one that is always used for screening new developments.
3. The old coreactant is removed and the new one dropped in. Perhaps a few small changes are made.
4. The system is passed through the standard set of tests.
5. If the performance is improved, the formulator may be interested enough to start some optimization. Or, as is typically the case, the performance drops or stays the same, the new coreactant is rejected on the first round.

This process is reproduced many, many times through out the industry, new products are developed and most result in either insignificant or no improvement in performance and may even reduce performance. Does this mean most of the best materials have already been invented or could it be a result of not having the time to really look? So if we ask why a new material is rejected then we have to consider:

A. The new material may not be better through some inherent characteristic.
B. We are testing it for the wrong use, and it may be better for another application
C. The use of an existing formulation may have defeated it.

Answers “B” and “C” should trouble anyone who is involved in development. These are events that may mask or impede a breakthrough. Case “B” can be seen in materials that are developed for one application, but find the greatest use in relatively unrelated one. Usually alternative applications for a product are not realized because the requirements of the different fields are not generally known within an organization.

A closer look at “C” is required to understand what may have happened. The formulation was optimized around the old coreactant. It is possible that new coreactant may have significantly destabilized the formulation performance by a number of routes. Questions that should be asked before discarding the new material are:

- Was the crosslinker correct for this new chemistry?
- Were the additives compatible with the new coreactant?
- Was there a deviance of one of the ingredients from normal delivery specs?
- Was the solvent blend appropriate?
- If it was pigmented, did the new coreactant affect the dispersion step?

To avoid such concerns it would be preferable to have an experimental program that identifies potential problems and generates data in such a way that it is applicable to a

broad range of applications. However, with current practices, answering these questions requires resources that are not typically available.

Lessons from Drug Discovery

Twenty years ago the situation was the same in the pharmaceutical industry as we now find in the coatings industry. Organic chemists laboriously synthesized a limited number of compounds each week, these in turn were tested for activity by bio and medicinal chemists done using time consuming experiments. At that time, lack of faster and less labor intensive activity screening techniques was a major bottleneck in drug discovery.

With the advent of cell or receptor based *in-vitro* assays the synthesis of suitable drug candidates all the sudden became the major bottleneck, which lead to the development of parallel and combinatorial synthesis methods. In the last decade we have witnessed a revolution in pharmaceutical research through the rapid development and application of ever better tools for automated synthesis and screening. Huge libraries of potential drug candidates and fully automated screening facilities working around the clock seven days a week are ubiquitous today. For example, Bayer Corporation Pharmaceutical Division, recently announced the opening of a new high throughput screening facility that can screen 200,000 drug candidates a day (1). The payoff of all these efforts is already visible on the horizon in the shape of an increasing number of patent publications for promising drug candidates. The focus of productivity improvement programs is now already shifting towards new challenges. The search is up for new drug targets for a wide variety of indications and considerable effort is put into genomics and proteomics programs as a means to find them. For a review on the development of the drug discovery process from a historical perspective see (2).

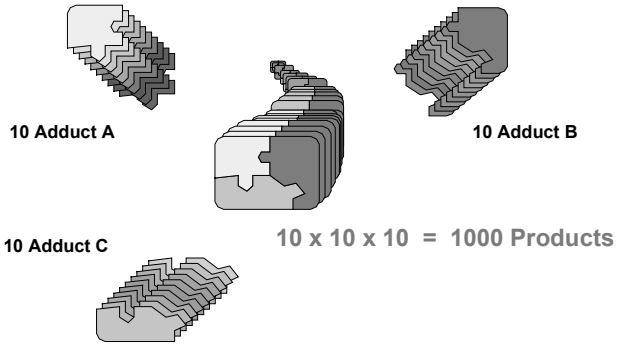
The driving force of the pharmaceutical industry's quest to increase productivity has been the high costs of bringing a drug from the first successful activity test in a cell based assay through the various development stages and clinical trails. While in the chemical industry improving the success rate of a given project may be worth tens of millions of dollars, the stakes are much larger in drug discovery. Conservative estimates assign costs on the order of half a billion dollars over a time span of 10 years to the development of a successful drug. Increasing the probability of success for a drug candidate entering clinical trials by carefully selecting the most promising molecule from a huge library can be worth hundreds of millions of dollars. Being able to stop a project before a drug candidate even enters clinical testing amounts in huge savings. Even greater value is realized from reducing the development time span between identification of a promising drug candidate and commercialization due to extended sales under patent protection.

What are the signatures of high throughput synthesis and screening that define today's drug discovery process?

(i) Experimental design strategies: There are a large number of functional groups and chemical structure types that have biological activity. Many of these have shown activity in drug therapy, with the activity being affected or driven by other groups that may be on the same molecule, and also by chirality, purity and delivery form.

When all of these factors are combined there are almost infinite variations available, with estimates of the possible structures ranging up to 10^{65} unique molecules of less than 1000 MW. Even when reducing the scope down to a few choices of different molecular fragments the possibilities are mind boggling. Significant effort is spent by the drug discovery groups on reducing the number of choices down to manageable "small" sizes. This is done by choosing a lead structure closely related to an existing active compound, using scientific intuition, or increasingly important through molecular modeling to predict activity of a certain arrangement of functional groups needed to plug into a receptor in the target cells. Once a chemical lead structure is identified a large number of derivatives – a library - is prepared based on that lead structure. The challenge lies in generating a library fulfilling certain diversity criteria, e.g. structural diversity, diversity of molecular weights, or diversity of lgP values, which describe the lipophilic character of a molecule.

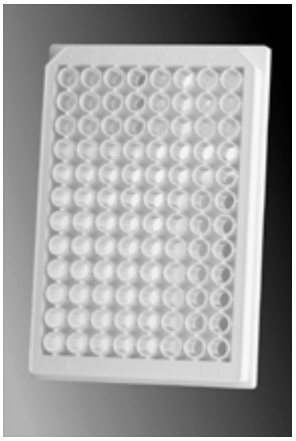
(ii) New synthetic methods and strategies: Solid phase synthesis, liquid phase synthesis, and split and pool synthesis are some of the widely used techniques for the synthesis of large compound libraries. A detailed discussion of these and other methodologies would go far beyond the scope of this article and the interested reader is referred to the scientific literature (3). A good starting point for further reading is *A Practical Guide to Combinatorial Chemistry* edited *by* Czarnik and DeWitt (4). The conceptual picture shown below gives an example on how the synthesis of a large number of compounds can be achieved quickly. The approach is based on conceiving a number of adduct types (determined by functionality) that react with each other in only one way. The adduct types are then systematically varied by changing the structures that are attached to the functional groups. For example "Adduct A" below could be a family of products with a reactive thiol group, and so on.

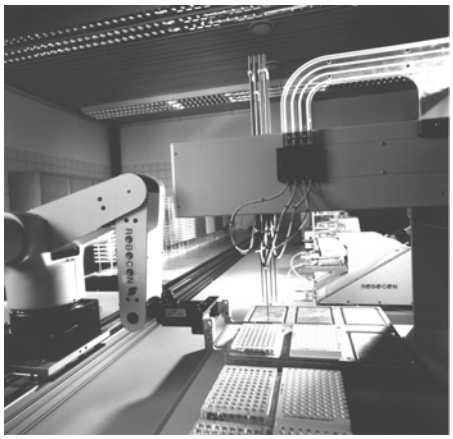


(iii) High throughput screening: With the possibility to generate thousands upon thousands of new compounds there is a need for high throughput screening techniques capable of characterizing them and testing their efficacy. A mere enumeration of the large number of techniques available would clearly go far beyond the scope of this article and the reader is again referred to the scientific literature for more details. Many of the efficacy screening techniques are optical

in nature and rely quite often on fluorescence probes to indicate whether or not a compound has affected the target favorably. For optical measurement such as fluorescence there are automated spectrometers available that can measure hundreds of samples in a matter of minutes.

(iv) Small scales, automation, and parallel processing: Synthesizing and testing of a large number of compounds poses some unique challenges with respect to instrumentation and workflow. Working with small sample sizes, using laboratory automation, and parallel processing are the key words here. Disposable 3 inch by 5 inch multi-well plates – usually called micro-titer plate - holding up to 1536 samples are used for sample storage and screening. Parallel liquid handling robots are employed for sample replication, other robots for loading plates into fluorescence readers or incubation ovens, and conveyor belts to carry plates from one place to the others.





Materials Science

Material Science is also on the verge of this fundamental change in the way products are developed. Based on a visionary concept by J.J. Hanak (5), inspired by the developments in the pharmaceutical industry, and led by the pioneering developments from Peter Schulz and the SYMYX Corporation, there are increasing reports of using combinatorial and high throughput techniques to develop new materials, new catalysts and new reaction conditions (6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16). The approaches being taken by investigators in this field challenge the imagination. As in drug research the number of compounds and size of reactions are not what is typically found in university training for chemists.

A multi-stage screening model for high throughput catalyst/material development put forward by Weinberg *et. al*. from Symyx Technologies (17) starts out with the testing of a library of 100,000 potential candidates in a primary screening (Figure 1). At this stage, just a few basic properties of the material/catalyst are tested using analytical techniques adapted to or specifically developed for high throughput experimentation. Out of this set several thousands leads may be found and tested further in a secondary screening. The best from this secondary screening are then developed by more

conventional methods to yield the final product. At this stage, the materials/catalysts are fully characterized using existing analytical techniques. Covering a large number of material candidates and reaction conditions in early stages of the screening increases the probability that the best candidates are found and further developed. In a conventional approach the development would start with the "standard lab reactor" in Figure 1. Of course, there is a much higher probability of failure, the assumption being that the screening reactions have removed the guaranteed failures or under performers.

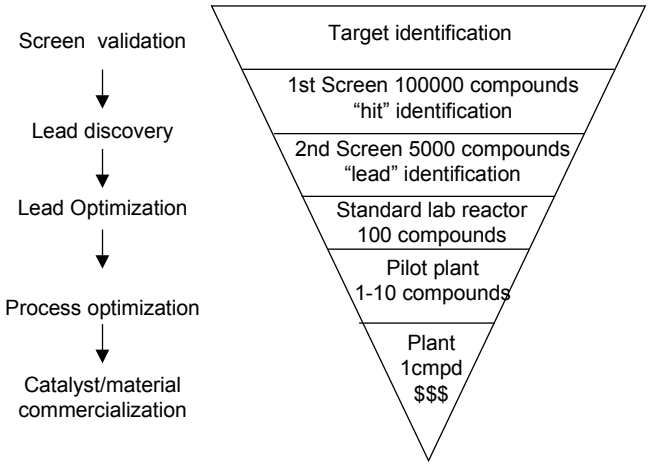


Figure 1. Process for discovery and optimization of materials (17).

For this process the target is usually identified by generalizing a known successful compound, or from molecular modeling. One of the first examples in this area was looking at superconducting ceramics (6) where Schulz and his coworkers started from the recently announced breakthroughs in the field. The compounds developed for the 1st screening are usually closely related in structure and represent a number of small iterations off of the target idea. For the superconducting materials this called for chemical libraries of systemic variations in the composition of Ba, Bi, Ca, Cu, Pb, Sr and Y mixed oxides. Those materials that showed promising conductivity on small scale were moved to the next stage and so on. This allowed for finding of products that could contain up to 5 of the metals in some proportion in the superconducting oxide product.

Many more examples of high throughput experiments in materials research are given in reference 17. These range from development of inorganic compounds for ferroelectric applications, catalysts, thin film insulators; to metal binding peptidic ligands and enzyme mimics; to organic polymers. For the inorganic materials, sputtering and vapor deposition techniques allow the formation of product libraries with thousands of compounds per square inch. Organic compounds and polymers are produced in sub-gram scale by the thousands. The applicability of this technology for the development of new materials is broad and very successful.

Key to the success in this area has been the development of analytical techniques for identifying when a successful hit is made. When looking at these types of experiments the key words are "fast" and "small", these being how the analyses are done and what the

size of the sample is. Many of the analytical techniques are optical type measurements where heats of reaction are measured by infrared thermography or chemical changes through color. There have also been devices described that can measure conductivity changes with micrometer resolution. Almost all of the techniques that have been used in high throughput material discovery are custom made.

Symyx Technologies has had the greatest success in moving towards standard analytical techniques. They have developed a common analysis platform for polymers that is integrated with their robotic discovery systems (18). This platform allows for the simultaneous or sequential measurement of 64 samples on a 2" x 2" substrate. Among the measurements they have adopted for this format are; Calorimetry; Dielectric Relaxation; Thermal Conductivity and Electronic Properties.

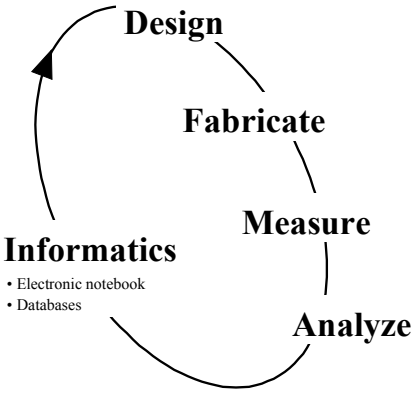
The Materials group at the National Institute of Standards and Technology (NIST) has taken on the challenge of looking at material properties of polymers using high throughput methodologies (12, 13, 14). This is important to coatings science for two reasons. First, they are studying fundamental aspects of polymer phase stability, adhesion, and surface properties. Second, they are developing standards for nomenclature and practices. For this discussion it is appropriate to structure the approach using the NIST group's framework for high throughput techniques by addressing the need to Design – Fabricate – Measure – and Analyze each experimental problem.

Design
- Using key variables/compounds available
- Using **experimental design strategies**
- Using statistical tools

Fabricate
- Using a **parallel** approach
- Working on **small scales**
- Using **automation**, e.g. liquid handling

Measure
- Measure **key properties** using automated assays

Analyze
- Using statistical analysis and visualization tools



How does this Apply to Coatings?

The outcome of any major investment in this area has to result in information that can guide a formulator to the proper choices, or instruct the synthetic chemists on how to change the chemistry of our products. When pondering the applicability of these concepts to coatings a number of questions come to mind.

First, do we have the diversity that demands high throughput methods?
Second, can we fabricate coatings in a high throughput manner?
Third, can we develop assays that allow us to measure meaningful values?

And finally, can we analyze the results of high throughput screening?

Design - Do coatings have the diversity?

The answer is a definite yes. Coatings are comprised of a number of ingredients and we have multiple choices for each one. Figure 2 shows a guide formulation typical of those provided by suppliers. It is for a white urethane "maintenance" topcoat, with a VOC of 2.8 lbs/gal. This formulation was developed by a supplier to demonstrate the capabilities of its resins. Is it fully optimized? Were all of the options looked at before release? Most likely the answer to the last two question is no.

	Wt	Supplier	Function
COMPONENT I			
Desmophen A LS-2945	359.40	BAYER	Acrylic Polyol
Caspol 5007	19.01	Caschem	Reactive Diluent
Ti-Pure R-960	327.00	DuPont	White Pigment
Novacite L-207	111.56	Malvern	Filler Pigment
Ircogel 906	31.55	Lubrizol	Rheology Modifier
Tinuvin 292	4.44	Ciba Geigy	UV Stabilizer
Anti Terra U	1.43	Byk Chemie	Dispersant
DC-56 (1% in Exxate 600)	7.08	Dow Corning	Flow Aid
Exxate 600	127.43	Exxon	Tail Solvent
Methyl amyl ketone	22.53	Numerous	Flash Solvent
COMPONENT II			
Desmodur N-3300	145.62	BAYER	Crosslinker
Total	**1157.05**		

Figure 2. Typical Guide Formulation, 2.8 VOC Acrylic Polyurethane Topcoat

The potential diversity of such a simple formulation can be understood by looking at the information provided in Table 1. Given a fixed resin system of the acrylic polyol and reactive diluent how many other options are there to be considered. For each of the other ingredients there are a number of different options. For example on the pigments a typical company will usually have 2 or 3 grades of titanium dioxide pigments and a number of filler pigments and grades within their list of authorized raw materials, so 10 is a reasonable number of choices that may be available. The same logic can be applied to the other ingredients, taking into account chemically different choices as well as supplier choices. Just to look at all the combinations without adjusting levels or blending would require screening 384,000 formulations (4x8x6x10x10x20).

Table 1. Potential number of choices in pigment maintenance topcoat

	Crosslinker	Flow Aids	UV Stabilizers	Pigments	Dispersants	Solvents
# Available	4	8	6	10	10	20
Blends/Levels	10	3	20	100	5	100
Total Choices	40	24	120	1000	50	2000

The situation becomes much more complicated when factoring in the number of potential blends and levels that each ingredient may be used in. This can be illustrated by considering a pigment dispersant. Usually it is prudent to run a ladder of 5 or so levels of a dispersant in a formulation to insure best performance. So to compare the 10 commercial dispersants available would require running 50 experiments without considering blends. When considering blends for all other ingredients as well, the potential number of formulations raises to 10^{13} (40x24x120x1000x50x2000).

These large numbers show that we have diversity, and that with a typical paint chemist making less than 100 experiments to optimize a formulation, we are not scratching the surface on the optimization front.

It is also important to understand how big a number 10^{13} really is. Even if we were to come up with a system that could test 200,000 formulations a day, it would take 150 thousand years to test all combinations. Clearly no business head has that kind of patience so there is still plenty of room for good science, intelligent design of experimentation and common sense.

Formulation diversity is just one level of the complexity provided by coatings. There is also a large selection of curing conditions, substrates and environmental conditions that need to be addressed.

Fabricate - Can we build realistic systems?

One of the big challenges of implementing a high throughput methodology is the number of systems that have to be put together and the sample sizes that are made.

Change from a weight to a volumetric approach – Preparing 1000 samples by methods traditionally used in the lab is very time consuming. The careful combination of products by weighing on a balance is time inefficient. Devices that automatically can pick up 1 gram of a wide variety of materials are not yet readily available. However, there are excellent, established methods for delivery of products volumetrically. Automatic pipettors have been developed for life science applications that will rapidly and reproducibly deliver liquids from the microliter scale up to 10's of ml's. State of the art systems are even fully computer controlled and dispense material based on values provided by spreadsheet.

Think Small – Making large numbers of samples is also problematic if the formulator continues to think in terms of pints and quarts for a typical sample size. Producing 1000 samples at a 1-quart size would easily fill a room and generate a large amount of waste. This also applies to the films that are going to be tested. It is not advisable to have your testing protocol require 6 X 9 panels, when testing several thousand systems. Preparing samples in the 5-10g size is straight forward using volumetric delivery devices and can be done in small sample vials. It is also possible to create the film test sample in the same type of vial, or the film can be cast in a microwell microtiter plate (Figure 3).

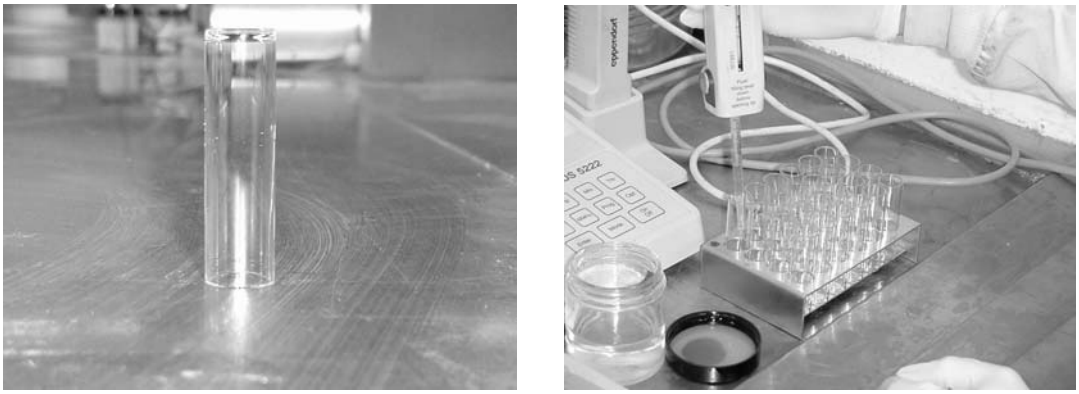


Figure 3. Small glass sample vial, sample dispensing with an automatic pipettor and in a multiplace rack.

After developing the skills for working with small formulation and samples sizes, the next step is to develop a workflow for using these techniques. As a theoretical exercise, we can look at testing a new "Melamine" crosslinker that has been developed. To evaluate this product it is required that it be formulated in systems which test:

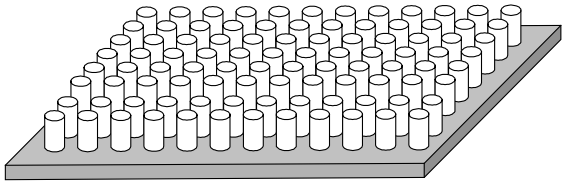
1. The crosslinker at different weight percents of total formulation
2. The crosslinker with a number of different catalysts at different levels
3. The films being cured at different temperatures for different time periods.

Figure 4 shows a possible workflow to accomplish this task. To start the polyol side is charged to 96 container holders (Figure 4A). These could be small vials in racks or wells in a large (3 ml per well) microtiter plate. The coreactant side would contain solvents and additives required for the formulation. To this base is added the new "melamine" crosslinker and solvent using a pattern as shown in Figure 4B. It is important to include control samples in each plate.

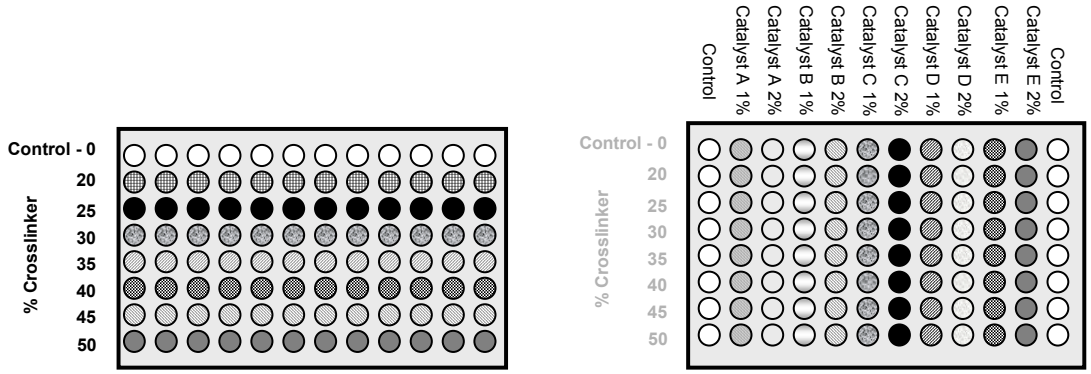
Films are then prepared by casting 50 microliters of solution into racks of small vials or microtiter plates for curing, use of a robot liquid handler allows multiple copies to be readily made (C). Each of the racks/plates contains the same set of formulations and are transferred to ovens for curing at different temperatures.

Figure 4. Potential steps in parallel formulation of new TSA melamine.

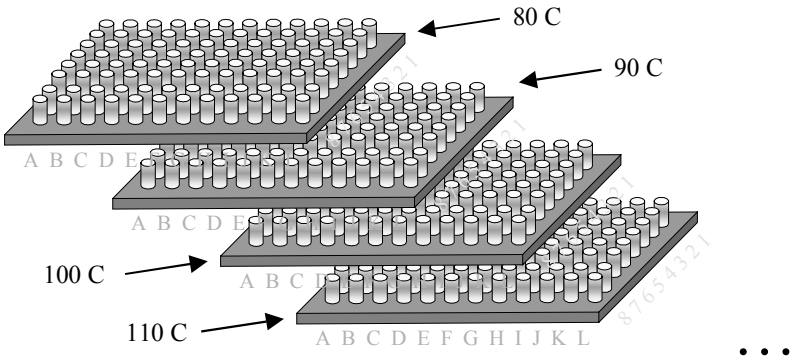
A. Fill 96 vials with desired coreactant, solvents, pigments and additives



B. Addition of Melamine Crosslinker at Different Wt Percents Addition of Desired Catalysts



C. Use a robotic liquid handler to make multiple copies of 50-100 µl into different arrays to test curing response, the copies are then baked at different temperatures (and times)



Measure – Can we get meaningful data?

The largest hurdle to implementing High Throughput techniques is the development of meaningful assays. The majority of the measurements that are made in the coatings industry are not appropriate for the size and number of samples produced using these methods. The industry is also partial towards applications specific tests that measure some property that is important to a particular end-use. These include measurements such as ASTM Gravelometer and ASTM Scrub Test, which are basically

meaningless outside the automotive and trades sales markets respectively. There is also wide spread use of subjective measurements that depend highly on the practitioner.

The sample size limits the applicable measurements. It is hard to imagine running MEK double rubs on a sample whose diameter is below 1 cm. Likewise that same sample size will thwart any attempt to measure hardness with a pencil or Koenig pendulum. Any technique that is a candidate for a High Throughput assay must be practical and relevant on a small sample.

The number of samples also has a major influence on the type of measurement being run. With an expectation of analyzing 100's if not 1000's of samples/day, the assay has to be highly automated. Too much human intervention will cause slow downs and could effect the measurement, not to forget the impact on the person doing the analysis. The high number of samples also calls for very fast assays, a slow process will greatly diminish the output.

One of the methods meeting these requirements that has been developed in the Bayer laboratories is based on solvent extraction of dyes from a film (19). This assay, shown in Figure 5, relies on the inclusion of a known amount of a non-reactive dye into the formulations. When a film is cast on a substrate, the dye is trapped within the film. After curing the film is placed in contact for a specified period of time with a solvent that can cause swelling to take place. If the swelling is sufficient, the dye is extracted. The solvent supernatant is then removed from the film and analyzed photometrically to determine the amount of dye extracted.

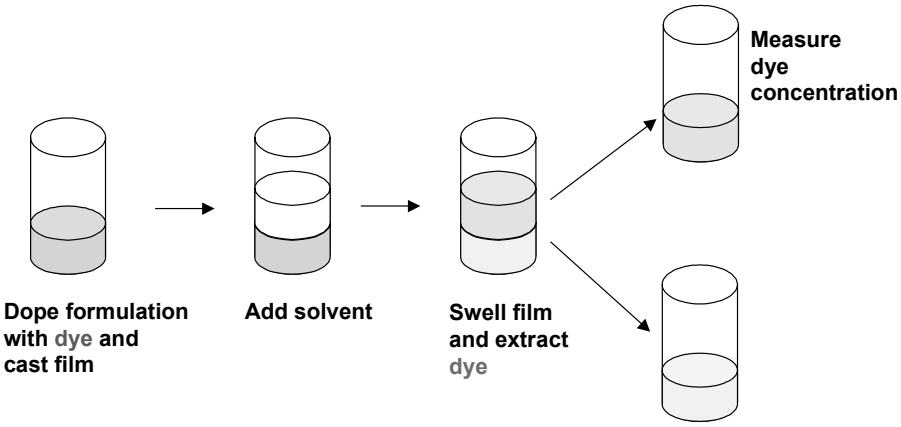


Figure 5. Schematic representation of solvent resistance by dye extraction.

The amount of dye extracted during the contact time with solvent correlates with the swelling degree of the film, which in turn correlates with its degree of curing. Higher dye extraction shows greater swelling, lower extraction comes from less swelling. By using a selection of solvents for this measurement, a quantitative value of solvent resistance is obtainable. This assay has been compared to results from DIN solvent spot testing on a large number of systems. The correlation between the visual DIN method and the dye extraction method was good, with the dye extraction giving a higher precision (1-100 scale, instead of the 1-5 visual scale) and no operator differences. This measurement

is a destructive one, it can only be run once on a given film because the dye concentration is reduced by the extraction.

This assay is particularly suited for monitoring curing in thermoset systems. If we applied this assay to a blocked polyisocyanate system a graph as shown in Figure 6would be found when compiling the results for a single formulation cured at multiple temperatures. After a low temperature bake a large amount of dye is extracted, with a high temperature bake yielding less. At one of the temperature settings there is a drastic reduction in the amount of dye extracted, indicative of the onset of rapid crosslinking.

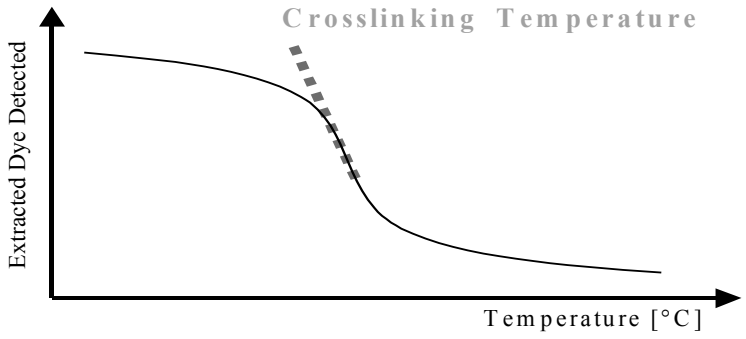


Figure 6. Level of dye extracted vs curing temperature for samples of a thermoset coating.

This technique was applied to blocked polyisocyanate-acrylic thermoset systems (20). The study looked at the effects of 130 different catalysts on the deblocking temperature of an hexamethylene diisocyanate (HDI) polyisocyanate blocked with 4 different blocking group. An acrylic coreactant was formulated with a variety of blocked HDI polyisocyanates and catalysts, following a methodology similar to that described for the theoretical melamine system described earlier. Multiple copies of the film arrays were made in small vials, baked at different temperatures for a fixed period of time. All systems were then evaluated using the dye extraction assay using a robotic liquid handler.

A representative result from this study is shown in Figure 7. Shown are the dye extraction curves for a dimethyl pyrazol blocking agent with 6 different catalysts. It is apparent that changing the catalyst has an effect, with DBTL having the largest. From this data one would expect to find that a DBTL catalyzed formulation (●) will cross-link at 50° C lower than the uncatalyzed one (✚). These match very well with published results for DMP blocked polyisocyanates that were studied using conventional techniques (21).

Film curing can also be monitored in situ in a high throughput fashion using dielectric spectroscopy (22). In a conceptual study employing a sample array of 10 films it was found that the evolution of the film conductance relates to its hardness and the evolution of the loss factor can be related to dry times.

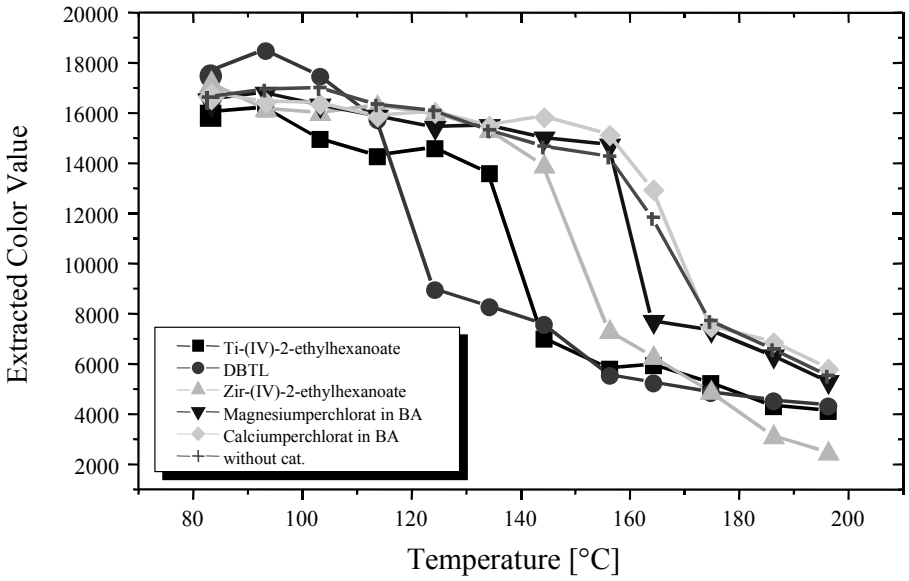


Figure 7. The effect of catalyst on the crosslinking temperature of an acrylic / DMP blocked HDI polyisocyanate system.

Another interesting method for characterizing the moisture permeability of films in a high throughput fashion was recently submitted for a patent (23). This assay uses a composite substrate (Figure 8.A) in which a template with circular holes is glued to a thin PET film. On the back of the PET film is a layer of material containing a moisture sensitive dye. Uniform films are cast into the wells (B), cured and then the front surface is exposed to saturated water environment for a specified period of time. Films that display high moisture permeability will be identified by a change in color on the back layer (C).

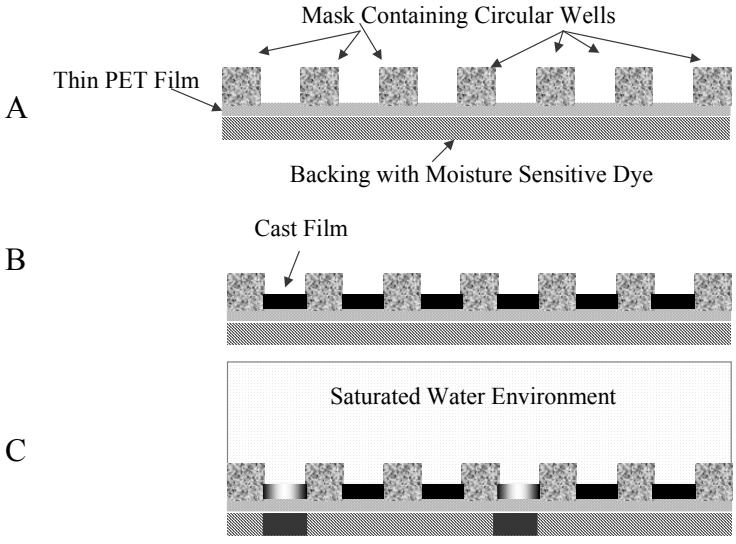


Figure 8. Method for testing the vapor permeability of thin films.

Analysis – Can all the data be interpreted meaningfully?

After developing the capability to fabricate a large number of samples, and developing the assays to measure the properties that are of interest, it is time to analyze the results. This is conceptually the most difficult part of High Throughput Screening for most new practitioners. In the laboratory it is common to sort and rank results from a couple of side by side experiments, and occasionally a group will attempt to rank several hundred competitive experiments. But when it comes to sorting through 1000's or 10,000's, our current approaches drop by the wayside. Just documenting the raw data by current methods would take days or even weeks.

As an example, a HTS experiment was run to evaluate a series of waterborne crosslinkers with a wide selection of polyurethane and acrylic dispersions (24). This study addressed 7 independent variables of a simple formulation of crosslinker plus dispersion (Figure 9). To address these variables 10,656 separate experiments were performed in triplicate resulting in more than 32,000 cast films. Keeping track of this was only possible through extensive use of complex computer data- bases that linked the formulation information with the assay results without manual entry of the individual numbers.

Resins		**Cross-linkers**	**% cross-linker on solids**	**Base for pH adjustment**
Bayhydrol 110 *	Lab. Product 2 *	CX-100 ♦		
Bayhydrol 121 *	Lab. Product 3 *	Desmodur XP 7063 *	4% and 8%	NH_4OH
Bayhydrol 123 *	Minwax polyacrylic •	PFAZ 322 *		n-methyl morpholine
Bayhydrol 2273 *	Lab. Product 4 *	XAMA2 *		TEA
Bayhydrol 2917 *	Lab. Product 5 *	XAMA220 *		
Bayhydrol 2952 *	NeoCryl A-639 ♦	XAMA7 *	**Time after blending**	**Dye- stock-solution**
Bayhydrol PR435 *	NeoCryl A-640 ♦	XAMA720 *		
Bayhydrol XP 7110 *	NeoRez R-940 ♦	none		Butyl-Cellosolve
Carboset CR-720 +	NeoRez R-9637 ♦	Ucarlink xl 29 se ♠	1h, 5h,	none
Carboset CR-785 +	Sancure 1514 +		1,2,3,6 days	
Dispercoll U 8713 *	Sancure +			
Dispercoll U 8758 *	Sancure 850 +		**pH**	
Dispercoll U 53 *	Street Shine #			
Easy Street #	Lab Product 6 *		as supplied (~7-8)	
Impranil DLV *			as supplied+2 units	
Lab. Product 1 *				

Figure 9. Variables in 2-component waterborne crosslinking study. (Suppliers: *=Bayer, +=BF-Goodrich, #= Basic Coatings, •=Minwax, ♦=NeoResins (Avecia), ♠=Union Carbide)

Analysis of such a study requires the use of advanced statistics and visualization software, the details of which are far beyond the scope of this paper. A flavor of the challenges is demonstrated in the graph of the data using the Spotfire® visualization software package. Figure 10 is a presentation of all of the dye extraction assay data from the crosslinking study sorted by the dispersion that is being crosslinked. The data is presented as a relative value, such that the value obtained for the crosslinked dispersion is divided by the value obtained for the same dispersion uncrosslinked. Thus a relative intensity of "1" shows no improvement in solvent resistance, while a value < 1 shows improvement.

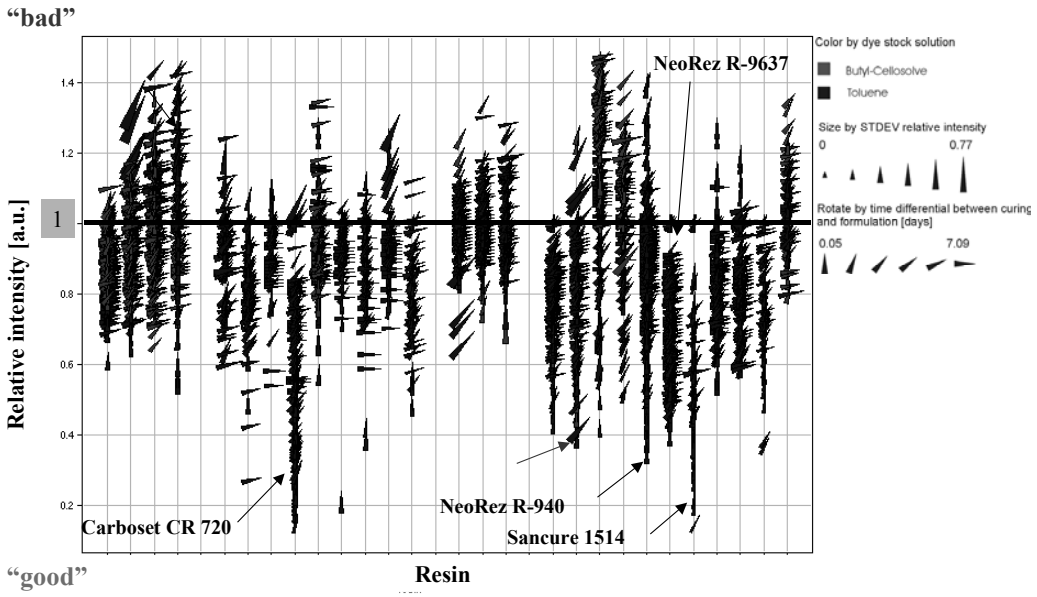


Figure 10. Plotting of relative dye extraction data for 2-component waterborne study.

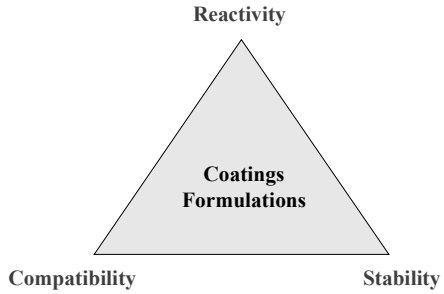
Such complex graphing capability is required to fully visualize the breadth of the data. With experience, the shape, position and width of the data groupings allows for quick evaluation of which resin is best, and how good the data is. Further statistical analysis identifies which factors are most important for the different resins and what if any 2nd or higher order interactions are present between the variables.

Limitations and Applicability of the Technology

These techniques are not a remedy for all what is wrong the coatings industry. They will not replace the tried and true methods of spraying panels and parts. They will not replace the need for skilled paint formulators. Miniaturization will not solve problems that can't be solved on normal scale.

The real use of this technology is given in the word "screening", it is a filter that should be designed to allow as many component candidates as possible to be fed in, but only the best candidates to come through. This screen should remove those candidates that cause a formulation to fail outright or do not show improvement. The focus has to be on greatly increasing the probability of success once the project shifts into full-scale development.

Within our activities we have focused developments on what are perceived to be universal "knockouts" for exclusion of a raw material from a formulation. Conversely improvement in one of these areas over the existing standard is a reason to move forward. These first line knockouts include negative effects on:



- Reactivity – how fast does a curing reaction (e.g. a cross-linking reaction) go and what is the degree of curing
- Compatibility – are the materials miscible, phase separated, do they result in hazy films
- Stability – does the formulation have shelf life.

These three topics cause much of the problems when optimizing formulations. Reactivity is drastically affected when there are interactions between additives and catalysts. It is not uncommon to see pigment dispersants negatively affect metal-carboxylate catalysts. Compatibility is also an issue, many resins are incompatible, but also many additives are. Phase separation by additives negatively affects gloss, DOI and can result in undesirable haze. The compatibility may also be affected by application conditions, a system which is fine under normal laboratory conditions may develop severe hazing when applied at high humidity conditions or at low temperature. Stability is the major stumbling block for formulations. Many times systems have been put together that meet all of the requirements when initially put together, but fail after storage for 6 months.

The reactivity can be measured using the previously described dye extraction assay as a function of time and temperature. Also available are infrared imaging techniques that measure the exotherms from reactions in arrayed form.

Compatibility of unpigmented systems is effectively determined by measuring film or solution clarity. In films, for example, looking at two sets of blends made with polyurethane and acrylic dispersions tested this concept. The first set was a series of different ratios of known incompatible materials; the second had the same ratios of compatible dispersions. Films were cast into a clear-bottom microtiter plate (Figure 11) and dried at room temperature. These castings can also be made in small glass vials. Visual inspection of the microtiter plates showed that phase separation had indeed taken place in the samples.

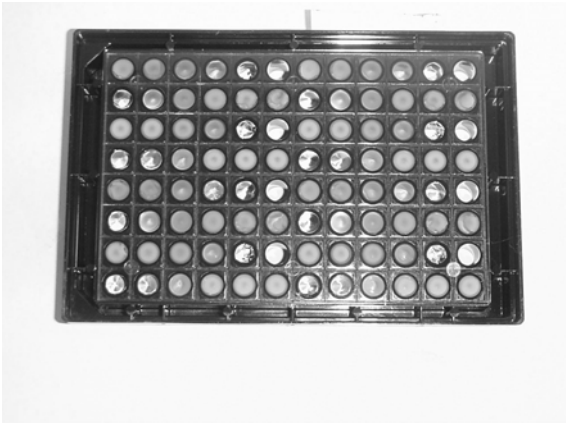


Figure 11. Bottom view of microtiter plate with cast polyurethane/polyacrylate films. Hazy surfaces represent incompatibility, shiny surfaces-compatibility.

The visual inspection only gave a subjective feeling for the level of haziness, a quantitative measurement could be obtained by measuring the opacity in a spectrophotometer designed to handle microtiter plates. Figure 12 contains representative results of this measurement and clearly differentiates between the two systems. The compatible system has an absorbance of less than 0.1 of the incident light across all ratios, while the incompatible system shows a marked increase in absorbance progress from either the pure acrylic or the pure polyurethane. The results match those expected in conventional evaluated blends.

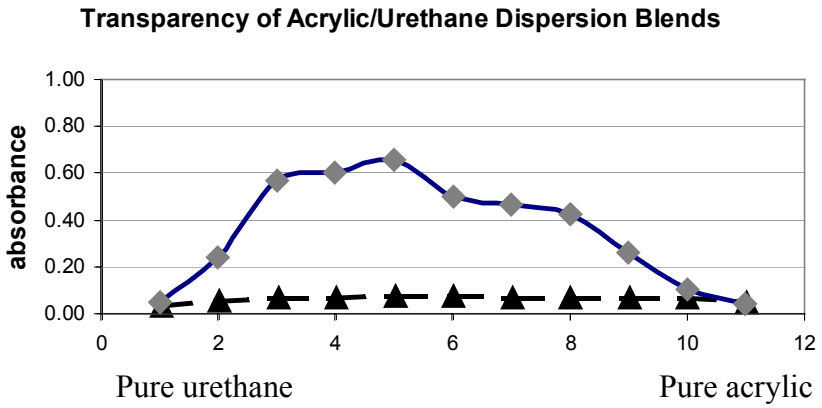


Figure 12. Comparison of the absorbance of an incompatible blend acrylic/polyurethane blend (◆) and compatible (▲) one as a function of composition.

Expanding the view of the compatible series shows the sensitivity of the measurement. The results from 4 independently cast sets of films are shown in Figure 13. The measured values are essentially the same from film to film within a given composition. It is also apparent that though still visually clear there was an increase in haziness resulting from the blending.

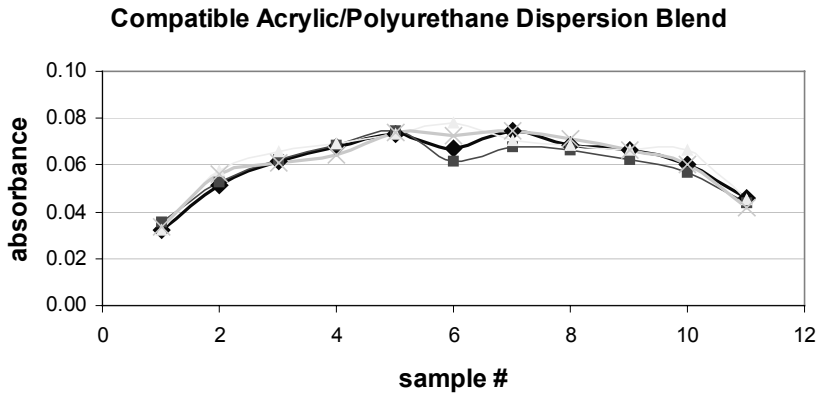


Figure 13. Expanded view of compatible acrylic polyurethane blend.

The stability of formulations is also straightforward. Application of the reactivity and compatibility tests as a function of storage time, will indicate whether or not significant degradation is taking place over time. It is also possible to measure indicators of formulation instability like the viscosity of the stored formulation.

Film stability is a concern when looking at over-bake conditions (heat stability) or exposure to different environments (water). This can also investigated by using the dye extraction test – a change in dye release could indicate breakdown of the film. It is also possible to probe this with the light transmission measurements, changes in transmission and/or color indicates something undesirable is going on in the film.

Challenges for the Future

Despite the impressive success stories that have been presented in the scientific literature and on conferences throughout the last few years there are major challenges ahead of us. Some of these are quite universal concerning methodological aspects relevant to all branches of materials research. Some apply more specifically to organic coatings.

Design

- Defining diversity – Within the drug discovery programs there has been great progress on defining structural group activity and what variations are required to get good diversity around a target molecule. Similar efforts will need to be undertaken for materials. The challenge posed to materials research seems to be even more difficult since – in contrast to drug discovery – we are not dealing with individual low molecular weight molecules but with synthetic polymers, mixtures, and process variables. What would be a diverse library of material components and process parameters in the light of synergistic effects that might finally lead to a superior material?

Fabrication

- Many properties of coatings depend on the fabrication methods used in preparing the formulation and its application to the substrate. On small scales the replication of the thermal and shear history of different mills used with pigment dispersion will not come easily. For the application side, being limited to film cast without considering the effects of spraying, brushing or rolling, leaves a large unknown to be addressed in conventional testing. Efforts need to be put both into automated and reproducible sample preparation methods as well as sample characterization techniques on small scales.

Measure

- In contrast to the screening of drug candidates where assay readings usually revolve around a simple yes or no answer, an interesting new material usually needs to exhibit a certain property profile comprising quite often 20 or more properties. Assays at least for some fundamental properties of materials need

to be developed. There are only a few coating specific methods that have made it into the open literature. Many more will be needed before there is general applicability of high throughput screening techniques.

- Standardization of assays – Standardization is a fact of life in all industries. The ASTM and other institutions strive to make our test results interchangeable and to ensure that they can be traced back to proven methods. There will be a great need to come up with the same discipline for high throughput screening to allow for sharing of results and cooperative developments between raw material suppliers, coatings manufacturers and the end user.

Analysis

- What level of detail is needed when dealing with huge multi-dimensional data sets? How can the huge amount of information turned into knowledge?

Cost

The cost of entry is very high. Pharmaceutical companies may spend 10's of millions of dollars to set up labs. Though not as much is required for a coatings application, the cost will still be beyond many companies financial resources and other companies risk tolerance.

- Equipment – Much of the equipment has to be custom developed to for each new assay or application. There are no off the shelf high throughput equivalents to a Zahn Cup series on the market.
- Databases and IT infrastructure – The implementation of Design, Fabrication, Measurement, and analysis using IT based concepts like electronic notebook keeping along with searchable databases is crucial. The support functions for these are not present within many small to medium coatings companies. There is no general system that is on the market, so the implementation is still custom development.
- Training and experience – Our schools are not producing graduates whetted in this technology, the experience will not be found in existing staff and there are not many skilled personnel to be hired away from the competition. It will take time and money to allow for the development of the required knowledge base to be successful.

Conclusions

High Throughput Screening, with it's related technologies, are upon us and are relevant to our field. The outcome of any major investment in this area has to result in information that can guide a formulator to the proper choices, or instruct the synthetic chemists on how to change the chemistry of our products. Initial ventures into the field show promise in screening formulations to identify key factors in reactivity, compatibility

and stability. Work now underway at a number of laboratories will extend the technology into screening of physical, mechanical and thermal properties.

There are many technical challenges to be met. They are not insurmountable, the lessons from other industries shows that the unimaginable can be accomplished when innovation is allowed to flourish.

The biggest challenges wait at the beginning and the end of the process:

- Defining diversity and its impact on what should be done and
- understanding and learning from what has been done.

Acknowledgements

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References

1. Bayer Corporation Press Release dated 11 May 2000

2. J. Drews, *Science* 2000, **287**, 1960.

3. N.K. Terret, M. Gardner, D.W. Gordon, R.J. Kobylecki, and J. Steele, *Tetrahydron* 1995, **51**, 8135.

4. "A Practical Guide to Combinatorial Chemistry", A. W. Czarnik and S. H. DeWitt eds, ACS 1997.

5. J. J. Hanak, *J. Mat. Sci* 1970, **5**, 964.

6. X. D. Xiang, X. D. Sun, G. Briceno, Y. Lou, K. A. Wang, H. Chang, W. G. Wallace-Freeman, S. W. Chen, and P. G. Schulz, *Science*, 1995, **268**, 1738.

7. E. W. McFarland, W. H. Weinberg , *Trends Biotechnol.* (1999) **17**(3) 107, J. D. Hewes, *CHIMICA OGGI/Chemistry Today*, **8/2000**, 20.

8. J.Wang, Y. Yoo, C. Gao, I. Takeuchi, X. Sun, H. Chang, X.-D. Xiang, P.G. Schulz, *Science*, 1998, **279**, 1712.

9. R.B. van Dover, L.F. Schneemeyer, and R.M. Fleming, *Nature*, 1998, **392**, 162.

10. E. Danielson, M. Devenney, D.M. Giaquinta, J.H. Golden, R.C. Haushalter, E.W. McFarland, D.M. Poojary, C.M. Reaves, W.H. Weinberg, X.D. Wu, *Science* 1998, **279**, 837.

11. E. Reddington, A. Sapienza, B. Gurau, R. Viswanathan, S. Sarangapani, E.S. Smotkin, T.E Mallouk, *Science* 1988, **280**, 1735.

12. J. C. Meredith, A. Karim, and E. J. Amis, *Macromolecules*, 2000, **33**, 5760.

13. J. C. Meredith, A.P. Smith, A. Karim, and E.J. Amis, *Macromolecules* 2000, **33**, 9747.

14 A. J. Crosby, A. Karim, E.J. Amis, *Polymer Preprints* 2001, **42**(2), 645.

15. S.M. Senkan, *Nature* 1998, **394**, 350.

16. S. Brocchini, K. James, V. Tangpasuthadol, J. Kohn, *JACS* 1997, **119**, 4553.

17. B. Jandeleit, D. J. Schaefer, T. S. Powers, H.W. Turner and W. H Weinberg, *Angew. Chem. Int. Ed.*, **1999**, 38, 2494.

18. P. Mansky, *Polymer Preprints*, 2001, **42**(2), 647.

19. H. Bach, Ch. Guertler,patent application pending, Bayer A.G.

20. H. Bach, Ch. Guertler, and S. Nowak, API-E Conference, Potsdam, Germany, October 2001, manuscript in preparation for publication in *Farbe&Lack*.

21. Th. Engbert, E. Jurgens, and E. Konig, *FATIPEC Congr.* (1996), **23r**d(Vol. B), B115-B143.

22. T.M. Santosusso, C.B. Walsh, and X. Gao, Poster Presentation 2000 Athens International Conference on Coatings Science and Technology, Vouliagmani, Greece and private communication.

23. US Patent Application 20010034063, Avery Dennison Corp.

24. H. Bach, unpublished results